

REMARKS

I. Introduction

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Upon entry of this Amendment, claims 1-12 will remain pending in the application.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Response to Issues Raised by Examiner in Outstanding Office Action

a. Claim Rejections - 35 U.S.C. § 102 and § 103

Claims 1-3, 6-8, 11 and 12 remain rejected under 35 U.S.C. § 102, as being anticipated by Luo et al. (US Publ. No. 2001/0051166). In addition, claims 4-5 and 9-10 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Luo in view of Sintov (WO 02 09763). Applicants respectfully request reconsideration and withdrawal of the rejection. Regarding the anticipation rejection, the Office re-asserts that Luo describes numerous elements found in the rejected claims. Office Action, pp. 2-4 and 7-8. In addition, the Office asserts that Sintov discloses a transdermal delivery system in hydrogel form as well as certain guar based polymers and non-ionic surfactants rendering those claims which are not anticipated by Luo obvious over Sintov. Office Action, pp. 4-5 and 7-8.

The Supreme Court has recently reaffirmed the *Graham* factors for the determination of obviousness. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ____ (2007) (holding that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions). These four factual inquiries under *Graham* are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 17-18 (1966). In accordance with these factors, to establish a *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or

suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert that this burden has not been met.

Applicant's do not believe Luo is relevant to the current application and does not teach or suggest the invention as claimed. More specifically, Luo et al disclose a transdermal drug delivery system based on a hydroxide-releasing agent, i.e., containing a base that elevates the pH of the system as well as of the skin to a pH above 8. According to Luo "it has now been discovered that hydroxide-releasing agents are highly effective permeation enhancers...." See paragraph [0007] of Luo. In contrast to Luo, the present invention is an enhancer-free microemulsion (see provided definition below), which acts as a thermodynamically-stable carrier for various drugs through the skin barriers and without the need of additives.

The preparation of a microemulsion generally requires the use of a co-surfactant. The inclusion of a co-surfactant does not create the art by itself. In other words, in many combinations of oil, water and surfactants no microemulsions are formed, only upon appropriate ratios and with selected oil and surfactant, the co-surfactant might form the transparent microemulsion system (spontaneously – with no energy involved). Most of the combinations form unstable coarse emulsions (if they are not homogenized or micronized by high-shear techniques), or separated two-phase systems. As explained in previous responses, the present invention uses tetraglycol for the first time to form microemulsions and the present system has been specifically designed utilizing ingredients to form microemulsions as described in the attached ternary phase diagram. Exhibit 1, white areas are the region of microemulsion existence, see below. Luo does not mention any use of a microemulsion (only what is called coarse emulsions), but does mention in one example the use of tetraglycol in a transdermal patch system. In this example, Luo (in Table 10, Example 4) used a mixture of tetraglycol, methylal (solvent with b.p. of 44 °C) and water (for NaOH) as a solvent system to dissolve ketoprofen, adhesive, NaOH and other components in the formulation to obtain a true solution (not an emulsion). Then the solution "was coated onto a release liner and dried in an oven at 55°C for two hours to remove water and other solvents." Such a system without a water phase cannot be called a 'two-phase system' or 'emulsion'. Applicants note that in

the control/blank patch, which did not contain NaOH, no water was required and, therefore, was not added from the beginning (Table 11).

Applicants direct the Office's attention to the bottom Figure in attached Exhibit 1. In this Figure, the microemulsion of the present invention was surprisingly found to deliver higher concentrations of drug across the skin, while the corresponding coarse emulsion (macro-emulsion containing tetraglycol), micellar system (containing tetraglycol), or the surfactants/cosurfactants alone did not deliver a significant amount of drug through the skin. This finding indicates that the system, which is disclosed in the present application, is neither taught or suggested by other tetraglycol-containing systems (that are not microemulsions), and shows that the current invention is nonobvious due to the unexpected results showing the surprising superiority of the current claims over other systems.

i. Microemulsion

The Office has requested a precise definition for microemulsion in order to clarify the distinctions with the prior art used by the Applicant. Today, the term has a specificity and uniqueness to those of skill in the art. In order to better present the scientific meaning and understanding of the term "microemulsion" over other known pharmaceutical systems, an article by S. Tenjaria in Critical Reviews in Therapeutic Drug Carrier Systems (16:461-521,1999) is helpful in providing a more precise and practical definition.

To avoid confusion in the terminology, for this application Applicants use the definition of Danielsson and Lindman (The definition of microemulsion, Colloid Surf., 3, 391, 1981) for "microemulsion:" A microemulsion is defined as a system of water, oil, and amphiphile which is [a] optically isotropic and thermodynamically stable liquid solution. By this definition, microemulsions DO NOT cover systems that are:

- (a) aqueous solutions of surfctants (micellar or nonmicellar) without additives.
- (b) aqueous solutions of surfactants containing only water-soluble nonelectrolytes as additives.
- (c) liquid crystalline phases
- (d) aqueous systems containing only inorganic electrolytes as additives
- (e) coarse emulsions, and

(f) systems that are surfactant-free.

Furthermore, it is generally accepted by those skilled in the art that emulsions are not really dispersions of components (as implied by the oil/water and water/oil terminology) but, to a much closer approximation, dispersions of the two phases into which the emulsion separate at equilibrium (Becker, P., Emulsion: Theory and Practice, Reinhold, NY, 1957; Sherman, P., Emulsion Science, Academic Press, NY, 1968; Lissant, K.J., Emulsions and emulsion Technology, Marcel Dekker, NY, 1974; Lissant, K.J., Demulsification, Marcel Dekker, NY, 1983).

Based on the above definition, Applicant notes that the current claims require the use of microemulsions and Luo does not describe or suggest the use of these microemulsions. Similarly, Sintov does not deal with microemulsions and, therefore, can not teach that tetraglycol can create microemulsions according to the present invention. Consequently, both references, even viewed as a whole, can not make the current claims obvious because they do not teach every limitation of the claimed invention. In light of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection.

b. Issues Under Double Patenting

Claims 1-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of co-pending Application No. 10/343,008 ("the '008 patent"). Applicants note that provisional rejections based on this ground are provided for in the MPEP, but should be removed when the rejection is the only rejection remaining in the application. See MPEP § 804. Applicants request removal of this rejection following reconsideration and withdrawal of the above rejections.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

It is acknowledged that the foregoing amendments are submitted after final rejection. However, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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